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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/412,558	10/05/1999	JUALANG HWANG	08919/022001	9802

26161 7590 07/08/2003

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	17

DATE MAILED: 07/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/411,558	Hwang et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jun 10, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *three* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s): _____

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Attachment.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*

Claim(s) objected to: *None*

Claim(s) rejected: *14, 15, 17, 18, and 24-27*

Claim(s) withdrawn from consideration: *None*

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

6/June 03

S. DEVI, PH.D.
PRIMARY EXAMINER
ART UNIT 1645

ATTACHMENT TO ADVISORY ACTION

After-Final Amendment

1) Acknowledgment is made of Applicants' amendment filed 12/10/02 (paper no. 13) in response to the final Office Action mailed 06/05/02 (paper no. 10).

Status of Claims

2) Claims 1-13, 16 and 19-23 have been canceled via the amendment filed 12/10/02.

Claims 14, 15, 17 and 18 have been amended via the amendment filed 12/10/02.

New claims 24-27 have been added via the amendment filed 12/10/02.

Claims 14, 15, 17, 18 and 24-27 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Finality of the Previous Office Action

5) Applicants allege that claim 17 was rejected in a new ground, i.e., anticipation by Hickey *et al.* (WO 97/15325). Applicants state that since this rejection was not initiated by Applicants' amendment to this claim in response to the Office Action dated 05 June 2002, the finality of the Office Action is improper.

It should be noted that claim 17 was in fact amended by Applicants via the amendment filed 12/10/02 (paper no. 13) which amendment changed the scope of the claim. As indicated in paragraph 17 of the Office Action mailed 03/10/03 (paper no. 15), Applicants' amendment to the claims (including claim 17) necessitated the new ground of rejection. Therefore, the finality of the Office Action mailed 03/10/03 is not premature or improper.

Rejection(s) Maintained

6) The rejection of claims 24-27 made in paragraph 11 of the office Action mailed 03/10/03 (paper no. 15) under 35 U.S.C § 112, first paragraph, as containing new subject matter, is maintained for reasons set forth therein.

Applicants argue that plasmid pPEDIG12, described in the paragraph bridging pages 10 and 11 of the specification, contains a DNA sequence encoding the receptor binding domain of *Pseudomonas* exotoxin A and 12 copies of GnRH repeats. Applicants assert that other portions of the PE DNA sequence is not included in the construct. Applicants submit that when determining whether a specification is in compliance with the written description requirement, the fundamental factual inquiry is that the subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement. Applicants conclude that based on the description of pPEDIG12 in the specification, a skilled artisan would understand that this plasmid excludes the sequence encoding the non-receptor binding domain of PE.

Applicants' arguments have been carefully considered, but are not persuasive. On page 10 of the specification, it is described that the plasmid used in the invention expresses a polypeptide 'containing' domain Ia of PE, which 'includes' the toxin receptor binding domain of the toxin and 'contains' a His_6 tag. This open language does not imply that the non-receptor binding domain of the *Pseudomonas* exotoxin A is 'excluded'. This description is not equivalent to an exclusive scope or exclusive claim language. The rejection stands.

7) The rejection of claims 14 and 18 made in paragraph 12 of the office Action mailed 03/10/03 (paper no. 15) under 35 U.S.C § 102(e) as being anticipated by Lorberboum-Galski *et al.* (US 6,140,066, filed 24 March 1998, already of record) as evidenced by Burnie *et al.* (EP 0 406 029), is maintained for reasons set forth therein.

Applicants contend that it is well known in the art that 'not very peptide is antigenic'. Applicants state that Lorberboum-Galski's linker sequence, GGGGS, is not mentioned to be antigenic. Applicants submit that as a structural component of the antibody, the linker sequence is usually preferred to be non-antigenic. With regard to the teachings of Burnie *et al.*, Applicants state that Burnie's teachings indicate that only particular fragments of the disclosed stress protein is antigenic, but not any peptide, e.g., GGGGS.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth in paragraph 12 of the Office Action mailed 03/10/03 (paper no. 15), Lorberboum-Galski *et al.* disclosed a DNA sequence encoding a polypeptide comprising a full length *Pseudomonas* exotoxin A (PE) and copies or repeats of a peptide sequence, gly-gly-gly-gly-ser, in a consecutive series (see Figure 1; 'Brief Description' for Figure 1; first full paragraph under 'EXAMPLE'; and column 10,

lines 42-45). The peptide sequence is repeated three times (see last paragraph in column 2). That the prior art full length *Pseudomonas* exotoxin A 'comprises' a receptor binding domain of *Pseudomonas* exotoxin A is inherent from the teachings of Lorberboum-Galski *et al.* That the prior art 5 amino acid-long peptide sequence, gly-gly-gly-gly-ser, serves intrinsically as an antigen is inherent from the teachings of Lorberboum-Galski *et al.* in light of what was well known in the art. For instance, Burnie *et al.* disclosed that a peptide consisting of five amino acids serves as an epitope (see last paragraph on page 3). Contrary to Applicants' assertion, a prior art reference does not have to provide express teaching. The inherent or implicit disclosure of a prior art can be relied upon in the rejection of claims under 35 U.S.C § 102 or § 103. M.P.E.P 2112. Burnie *et al.* was applied to document the art-recognized size of an epitope. Burnie *et al.* demonstrated that a five amino acid-long peptide served as an epitope. Lorberboum-Galski's gly-gly-gly-gly-ser sequence is clearly long enough to serve as an antigen. Nothing in Lorberboum-Galski's patent teaches that gly-gly-gly-gly-ser is incapable of serving inherently as an antigen in addition to serving as a linker. Contrary to Applicants' statement, both an antibody and a structural component of the antibody such as a linker, do serve inherently as antigens and are capable of binding with specific antibodies. The rejection stands.

8) The rejection of claims 14, 15, 17 and 18 made in paragraph 13 of the office Action mailed 03/10/03 (paper no. 15) under 35 U.S.C § 102(b) as being anticipated by Hickey *et al.* (WO 97/15325 - already of record), is maintained for reasons set forth therein. The inclusion of claim 16 in this rejection in the last Office Action was an inadvertent error.

Applicants acknowledge that Hickey *et al.* disclosed GnRH-PE chimeric hybrid proteins produced using recombinant DNA technology. Applicants assert that in a GnRH-PE conjugate, multiple copies of GnRH can be attached to a scaffold and the scaffold is attached to PE. Applicants point to page 9, lines 29-32 and state that in a GnRH-PE chimeric hybrid protein, there may be two tandem repeats of GnRH.

Applicants' arguments have been carefully considered, but are non-persuasive. Hickey *et al.* taught an immunogenic carrier system comprising a *Pseudomonas* exotoxin and GnRH, produced either by chemically coupling a GnRH to PE, or by recombinant DNA techniques to produce GnRH-PE hybrid proteins (see page 12, lines 8-11). Hickey's immunogenic carrier system exists with or *without* the scaffold. The PE used by Hickey *et al.* included PE variants or fragments (see page 10).

While only one immunogenic carrier system exemplified on page 9 is described as containing two GnRH molecules, the number of GnRH (X) in the disclosed immunogenic carrier system is taught to be 2 times 1 to 10 (r), i.e., 2 through 20 GnRH. See page 13. Therefore, more than two GnRH molecules are not excluded in the Hickey's immunogenic carrier system, which includes GnRH-PE chimeric hybrid proteins produced by using recombinant DNA technology. Hickey's hybrid proteins contain contiguous sequences of the constituent proteins or peptides encoded by recombinant DNA sequences (see pages 20, 29 and 30). The rejection of claims 14, 15, 17 and 18 as being anticipated by Hickey *et al.* stands.

9) The rejection of claims 24-27 made in paragraph 14 of the Office Action mailed 03/10/03 (paper no. 15) under 35 U.S.C. § 103(a) as being unpatentable over Hickey *et al.* (WO 97/15325 - already of record) in view of Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989) and Pastan *et al.* (US 4,892,827 - already of record), is maintained.

Applicants contend that the number of PE variant is enormous and that it can be any fragment of PE, any insertion, deletion or substitution mutant of PE, or any chemically modified molecule of PE. Applicants allege that none of the three references, Hickey *et al.*, Hwang *et al.* and Pastan *et al.*, provides a reason why, among the numerous PE variants, domain Ia should be chosen to replace the full-length PE protein encoded by the nucleic acid disclosed in Hickey *et al.* Applicants state that Hwang *et al.* only teach that the Ia domain of PE itself can be used for producing vaccines against PE-mediated diseases, but do not suggest that the Ia domain can be used as an antigen carrier to facilitate induction of immune response against the antigen. Applicants acknowledge that PE Ia is less toxic than the full-length PE protein, but submit that it appears not to be the choice of Hickey *et al.* Applicants point to the paragraph bridging pages 9 and 10, and allege that Hickey *et al.* teach *Pseudomonas* exotoxin variants having amino acids 1-252 (domain Ia) as the preferred variants. Applicants assert that Hickey *et al.* teach away from claims 24-27.

Applicants' arguments have been carefully considered, but are non-persuasive. First, it should be noted that instant claims are not drawn to a method of facilitating induction of immune response against an antigen using PE Ia domain as an antigen carrier. Hickey *et al.* taught an immunogenic carrier system comprising a *Pseudomonas* exotoxin and GnRH, produced either by chemically coupling a GnRH to PE, or by *recombinant DNA techniques* to produce GnRH-PE hybrid proteins (see page 12, lines 8-11). Hickey *et al.* taught the concept and the use of

incorporating 2-20 copies of GnRH in a fusion preparation and the use *of recombinant DNA sequences* for this purpose (see pages 20-22 and pages 29-31). Although one recombinant hybrid GnRH protein exemplified on page 9 contains two GnRH molecules, as explained above, Hickey's disclosure does not exclude the use of more than two tandem repeats of GnRH. Similarly, Hickey *et al.* do not exclude the PE domain Ia in the GnRH hybrid fusion. In fact, contrary to Applicants' assertion, in the paragraph bridging pages 9 and 10, Hickey *et al.* taught the preferred *Pseudomonas* exotoxin variants to be segments of *Pseudomonas* exotoxin wherein *the ADP ribosylating activity* has been attenuated or inactivated 'through deletion' of amino acids in the *ribosylating domain.* Thus, Hickey's disclosure explicitly includes, as a preferred embodiment, PE variants wherein the PE domain Ia is not deleted, but the ADP ribosylating activity region (i.e., non-receptor binding domain) has been deleted. Hickey *et al.* further specifically taught that the efficiency of PE as an immunogenic carrier is independent of the toxin activity of the PE. Hwang *et al.* do not have to teach or suggest that the Ia domain can be used as an antigen carrier to facilitate induction of immune response against the antigen, since the instant claims are not drawn to a method of using PE Ia domain as an antigen carrier to facilitate induction of immune response against the antigen. Moreover, as set forth above, Hickey *et al.* have expressly taught one of the preferred *Pseudomonas* exotoxin variants in their hybrid fusion protein to be the ribosylating activity region-deleted (i.e., non-receptor binding domain-deleted) PE variant. See paragraph bridging pages 9 and 10. Since Hickey alone provides the express teaching or suggestion, Hwang *et al.* and Pastan *et al.* do not have to provide a reason why, among the numerous PE variants, domain Ia should be chosen. Hwang *et al.* and Pastan *et al.* taught the plasmid or nucleic acid sequence encoding domain Ia of PE. While Hwang *et al.* specifically taught the use of domain Ia of PE for *in vivo* vaccination purposes, Pastan *et al.* specifically taught the diminished toxicity of domain Ia of PE and the fusion of part of PE with polypeptides, including luteinizing hormone. The rejection stands.

Pertinent Prior Art

10) The prior art made of record and not relied upon currently in any of the rejections are considered pertinent to Applicants' disclosure.

- The art has recognized that an epitope or antigenic determinant can comprise 3 or more, generally 5 amino acids, in a spatial conformation unique to the epitope. See paragraph bridging pages 14 and 15 of WO 93/18150 issued to Covacci *et al.*

Remarks

11) Claims 14, 15, 17, 18 and 24-27 stand rejected.

12) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

13) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

June, 2003

SD
S. DEVI, PH.D.
PRIMARY EXAMINER